EFFECT OF EPINEPHRINE ON THE LSD REACTION

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Many of the effects of LSD in animals and man suggest a state of hyperactivity of the adrenergic autonomic nervous system. Rothlin has postulated that LSD creates a central hyperactive autonomic state. Dille and his coworkers at the University of Washington found that phenoxybenzamine blocked LSD-induced hyperthermia and behavioral changes in animals. The same group found that administration of LSD two hours after reserpine resulted in marked augmentation of the LSD hyperthermia, whereas administration of LSD ten hours after reserpine resulted in little hyperthermia. Since reserpine is known to cause a discharge of serotonin and norepinephrine in the brain, the change two hours after reserpine might be correlated with a discharge of epinephrine and norepinephrine, whereas at ten hours these substances would be depleted in the tissues. In recent experiments we were unable to show any diminution in the intensity of the mental symptoms induced by LSD after pretreatment of human subjects with various doses of phenoxybenzamine. This result did not favor the adrenergic hypothesis. It was, therefore, thought desirable to determine the effect of epinephrine on the LSD-reaction since an accentuation of the effect of LSD would favor the adrenergic hypothesis.

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METHODS.

Subjects. Nine former-addict Negro males who were serving sentences for violation of the narcotic laws served as subjects in these experiments. Their ages varied between 21 and 38 years. All had been abstinent from morphine for several months. All had experienced the effects of LSD and were familiar with the mental changes produced by that drug.

Drugs. LSD was given orally as the tartrate in solution. The drug was administered at 8 a.m. to patients in the fasting state. Epinephrine hydrochloride was administered subcutaneously at 10 a.m. in doses of 0.4 to 0.6 mg./70 kg. These amounts had been shown to induce typical cardiovascular effects in the experiments involving phenoxybenzamine.

The following combinations were studied, using a randomized balanced Latin-square design: LSD plus epinephrine placebo; LSD placebo plus epinephrine 0.4 mg./70 kg.; LSD placebo plus 0.6 mg. epinephrine/70 kg.; 1 mcg./kg. LSD plus 0.4 mg. epinephrine per kg.; and, 1 mcg./kg. LSD plus 0.6 mg./70 kg. of epinephrine. A double-placebo combination was not included, since the important comparisons were those with LSD plus epinephrine placebo and LSD plus epinephrine.

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Observations. Pupillary diameter, resting systolic blood pressure, and threshold for kneejerks were measured as previously described. These determinations were made every hour on the hour from 7 a.m. to 4 p.m. An additional measurement was obtained at 10:10 a.m., ten minutes after subcutaneous administration of epinephrine and epinephrine placebo. This timing coincides with the height of the epinephrine-effect as determined in previous experiments. The modification of the Jarvik-Abramson questionnaire was administered to the patients every hour on the half-hour from 7:30 a.m. to 3:30 p.m., except questionnaire was administered at 10:20 a.m., after epinephrine rather thanaat 10:30 a.m. The clinical grades of the reactions were assigned by our usual system.

Analysis. The critical measures were those obtained at 10:00 a.m. (pre-epinephrine) and at 10:10 a.m. (height of epinephrine effect) plus questionnaires at 9:30 a.m. and 10:20 a.m. These values were tabulated and averaged.

Results are shown in the accompanying table. Since the differences between LSD placebo and LSD plus epinephrine were quite small and obviously nonsignificant, statistical calculations were not made. The figures do not indicate either inhibition or accentuation of the LSD reaction by epinephrine.

Discussion. Like the experiment with phenoxybenzamine, the results do not favor, but also do not disprove, the adrenergic hypothesis of the LSD reaction. In this connection, it is important to remember that epinephrine is known to have effects on the central nervous system (changes in the activity of the reticular activating system), so that the lack of effect is probably not attributable to difficulty in penetration of the blood brain barrier by epinephrine.

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EATMENT	MEASURE AND TIME												
	Pulse Rate 10 AM	Pulse Rate 10:10 AM	Blood Pressure 10 AM	Blood Pressure 10:10 AM	Pupils 10 AM	Pupils 10:10 AM	Knee-jerk 10 AM	Knee-jerk 10:10 AM	Questions 9:30 AM	Questions 10:20 AM	Questions Total	Grade 9:30 AM	Grade 10:20 AM
SD placebo lus epinephrine .4 mg./70 kg.	70	74	111	117	4.7	4.8	1.3	1.2	1	1	2	0	0
SD 1.0 mcg./kg. lus epinephrine .4 mg./70 kg.	80	84	122	126	6.6	6.7	2.3	2.6	17	17	67	2.2	2.2
SD 1.0 mcg./kg. lus epinephrine lacebo	69	66	117	124	6.2	6.2	1.6	1.6	11	12	49	1.33	1.56
SD placebo plus pinephrine .6 mg./70 kg.	72	77	119	118	4.9	4.7	1.0	1.3	1	0	1	0	0
SD 1.0 mcg./kg. lus epinephrine .6 mg./70 kg.	78	85	123	127	7.0	7.0	2.7	2.6	15	14	60	2.2	2.2

Figures are averages on 9 subjects.